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DOI:
10.1016/j.clnu.2017.09.004

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Citation for published version (APA):
Wright, J., & Baldwin, C. (2018). Oral nutritional support with or without exercise in the management of malnutrition in nutritionally vulnerable older people: a systematic review and meta-analysis. *CLINICAL NUTRITION*, *37*(6, Part A), 1879-1891. https://doi.org/10.1016/j.clnu.2017.09.004

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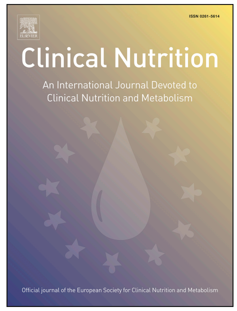

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PII: S0261-5614(17)30319-9
DOI: 10.1016/j.clnu.2017.09.004
Reference: YCLNU 3248

To appear in: *Clinical Nutrition*

Received Date: 27 April 2017
Revised Date: 31 July 2017
Accepted Date: 5 September 2017

Please cite this article as: Wright J, Baldwin C, Oral nutritional support with or without exercise in the management of malnutrition in nutritionally vulnerable older people: a systematic review and meta-analysis, *Clinical Nutrition* (2017), doi: 10.1016/j.clnu.2017.09.004.

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Oral nutritional support with or without exercise in the management of malnutrition in nutritionally vulnerable older people: a systematic review and meta-analysis

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Clinical trial registry number and website: This trial was registered at http://www.crd.york.ac.uk/PROSPERO/ as CRD42015027323.

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Abstract:

Background: Physical functioning declines with advancing age and compounds malnutrition, common in elderly populations. A dual-intervention combining oral nutritional support and exercise may delay these changes. Our aims were to assess whether exercise combined with oral nutritional support (ONS) has greater improvements on physical functioning, quality of life and nutritional status than nutrition intervention alone in nutritionally vulnerable older adults.

Methods: Three electronic databases were searched for randomised controlled trials of older adults judged to be: sarcopenic, cachexic, frail, malnourished, and/or at risk of malnutrition, receiving ONS and exercise compared to nutrition intervention alone. Meta-analyses were performed using a fixed-effect model to calculate standardised mean difference (SMD) (hand-grip strength, limb strength, gait speed, timed up-and-go test (TUG), physical activity level and fat-free mass) or relative risk (hospitalisation) with 95% confidence intervals (CIs).

Results: Eleven studies (n=1459 participants) were included. ONS and exercise interventions varied considerably between studies. There was very low quality evidence that exercise combined with ONS compared to nutrition intervention alone resulted in significant improvements in limb strength, (SMD = 0.33; 95% CI 0.13 to 0.53; P = 0.001) but low quality evidence of no effect on fat-free mass (SMD = -0.05; 95% CI -0.27 to 0.18; P = 0.70), physical activity level (SMD = 0.04; 95% CI -0.26 to 0.33; P = 0.81) and TUG (mean difference = -0.80; 95% CI -2.06 to 0.47; P = 0.22). Moderate quality evidence from a small number of studies found no effect on handgrip strength and QOL. Low quality evidence of faster gait speeds were found in participants receiving ONS alone compared to combined intervention (SMD = 0.38; 95% CI 0.19 to 0.56; P < 0.0001).

Conclusion: Combining exercise with ONS may provide additional improvements to muscle strength but had no effect on other measures of physical functioning, nutritional status or morbidity in nutritionally vulnerable older adults.

Key words

Oral nutritional support, exercise, older adults, sarcopenia, malnutrition, physical function

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1. Introduction

Risk of malnutrition increases with advancing age (54) and is associated with inadequate dietary intake (45) and increasingly sedentary lifestyles. These factors contribute to sarcopenia, an age-related decline of skeletal muscle mass, and physical function (19). Malnutrition and sarcopenia may be further compounded in older adults with underlying disease by cachexia defined as illness-related persistent and progressive loss of muscle with or without loss of fat mass (2, 26). Disability, frailty and morbidity are consequential of muscle loss (4, 33) and are associated with significant impairments to quality of life (QOL) (19) and increased costs of healthcare (34) underlining the need for appropriate intervention. Although many factors influence sarcopenia, malnutrition and physical inactivity (PA) appear to be most amenable to change. Thus, targeted nutrition and exercise interventions have the potential to attenuate and even reverse age-related decline in muscle decline (28).

Research consistently demonstrates nutritional intervention can reverse malnutrition but not cachexia (39), however its impact on sarcopenia lacks clarity. Observational studies and randomised controlled trials (RCTs) demonstrate nutritional support may *preserve* muscle mass but does not appear to increase it (1, 23, 27, 31, 57, 58, 64). Furthermore the effects on physical function appear limited. Two systematic reviews found nutritional intervention improved weight gain, nutritional intake and mortality in older people at risk of malnutrition and yet had no effect on functional status (44, 46). In contrast, the benefits of exercise on maintenance and restoration of muscle mass and functioning in frail, elderly populations is [1]widely recognised (63) and research has shown a positive impact on muscle strength and function (28, 50, 53, 59).

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[1] ADL, activities of daily living; BMI, body mass index; CI, confidence interval; EOI, end of intervention; FFM, fat-free mass; I^2, inconsistency; MD, mean difference; PA, physical activity;

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Separately, nutrition and exercise interventions seem to influence lean body mass and functional status, respectively, in frail, elderly populations. Combining the two could provide greater benefits than from either alone. A systematic review of the effects of nutritional supplements together with exercise training in healthy older adults identified eight RCTs and concluded that supplements were able to augment exercise-induced increases in muscle mass which subsequently improved functional status (60). The review suggests the potential for using multimodal interventions to improve physical functioning in older adults, however, its conclusions are based on a small number of studies, included only *healthy* adults and the nutritional supplements included varied from protein drinks and amino acid supplements to single micronutrients. Whether similar benefits from the use of combined nutrition and exercise interventions would be seem in frail and undernourished older people remains to be determined.

Accordingly, the present systematic review and meta-analyses of RCTs was undertaken to assess whether combining exercise and nutrition interventions leads to greater improvements in physical functioning, QOL, nutritional status, mortality, and morbidity compared to nutritional support without exercise in older adults judged to be sarcopenic, cachexic, malnourished, or at risk of malnutrition.

QOL, quality of life; RCT, randomised controlled trial; SD, standard deviation; SMD, standardised mean difference; TUG, timed up-and-go

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2. Materials and methods

2.1 Protocol and registration

A protocol was completed for the systematic review using Cochrane guidelines (17, 30) and submitted to PROSPERO International Prospective Register on Systematic Reviews (52); registration number: CRD42015027323.

2.2 Eligibility criteria

2.2.1 Studies

Included studies were RCTs conducted in acute and community settings, including cross-over and parallel designs. Observational, animal and quasi-experimental studies were excluded.

2.2.2 Participants

Older adults judged to be: *cachexic* from the presence of a chronic muscle-wasting illness including cancer and HIV/AIDS; *sarcopenic* as evidenced by age, loss of fat-free mass (FFM) or increasingly sedentary behaviour; *malnourished,* and/or at risk *of malnutrition* indicated by body mass index (BMI), weight loss, inadequate dietary intake or frailty, assessed by a screening tool or judged by the review author. No pre-specified age cut-offs were used because onset and rate of muscle ageing varies between individuals and noticeable muscle losses can occur anytime from the fifth decade (21, 32). BMI judgements were in line with Beck and Ovesen's (5) suggestion of using a higher BMI cut-off (BMI<24 kg/m^2) than the World Health Organisation's classification (62) and any amount of weight loss to facilitate earlier identification of malnutrition in over sixty-five's to reflect their finding that a weight loss of 5% annually was found to be clinically significant (5).

2.2.3 Interventions and comparisons

Eligible RCTs compared a combined intervention of oral nutritional support with exercise to oral nutritional support alone. No pre-specified criteria were set for appropriate duration, frequency, timing, intensity/dosage or delivery mode of either the exercise or nutrition interventions. Exercise consisted of advice-giving and/or delivery of exercise sessions. 'Oral nutritional support' encompassed dietary counselling, food fortification and/or use of oral nutritional supplements. Studies comparing exercise alone vs. oral nutritional support were excluded.

2.2.4 Primary outcomes

(i) Physical functioning assessed by: handgrip strength, limb strength, physical performance (gait speed, walking test, chair-stand test, balance test), ADL, PA score and functional score; (ii) QOL; and (iii) measures of nutritional status including: skinfold thickness, limb circumference, limb area and FFM were set as primary outcomes.

2.2.5 Secondary outcomes

Mortality and morbidity assessed by hospitalisation (admission or readmission) and length of stay.

2.3 Search strategy and study selection

Three electronic databases were searched to 5 October 2015 for publications of intervention studies including Ovid MEDLINE, Cochrane Central Register of Controlled Trials and Web of Science Core Collection (SCI-EXPANDED). The search was restricted to RCTs of human adults using electronic filters. No language restrictions were applied and abstracts of publications not in English but considered eligible were translated. The following key terms were searched: (*nutritional support* OR *diet** OR *nutrition** OR *food** OR *feed** OR *eat** OR

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*meal** OR *snack** OR *nutriment** OR *fortif** OR *nourish** OR *enrich** OR *energy dense* OR *protein dense* OR *nutritional supplement** OR *oral supplement** OR *high energy* OR *high protein* OR *nutritionally complete*) AND (*exercis** OR *physical** OR *active** OR *workout** OR *bodybuilder** OR *gym* OR *sport** OR *train** OR *coach** OR *strength*) AND (*aged* OR *old** OR *age-old* OR *elder** OR *senior*). The searches were refined by excluding *obesity*, *type 2 diabetes* and related terminology. In addition to electronic searches, reference lists of articles assessed for eligibility and PubMed's 'suggested related citations' of articles identified for inclusion, were searched and assessed against inclusion criteria.

The study selection process was carried out by the review author alone as part of an undergraduate dissertation but built on searches carried out by two previous students. All articles generated from the electronic search were imported into RefWorks (Proquest, Michigan, USA); a reference management software, and duplicates were removed. The titles of remaining articles were screened for eligibility based on inclusion criteria. All titles assessed as ineligible were excluded. Post-screening, the abstracts and full-texts of remaining articles were retrieved and reviewed to determine studies for inclusion. Any articles deemed ineligible at this stage were excluded and the reasoning reported. Of the eligible articles, multiple reports of the same study were linked together to determine a list of studies confirmed for inclusion in the systematic review. The list of studies identified for inclusion was then compared against the list of studies identified in previous similar dissertations to ensure that no studies had been missed.

2.4 Data management

2.4.1 Data extraction and assessment of risk of bias

Data extraction and assessment of risk of bias were carried out by the review author alone. The following details were extracted from each study: first author, year of publication, number of participants randomised, sex (percentage female), setting and country of participants, inclusion criteria, details of study design, intervention and comparator groups including frequency, duration, follow-up times, outcome variables measured and outcome data on physical functioning, QOL, nutritional status, mortality and morbidity with number of participants in each group. Where available, continuous data were extracted as: (i) mean change or percentage mean change plus standard deviation (SD), standard error of mean or 95% confidence interval (CI), or (ii) mean or median values plus SD, standard error of mean or interquartile range at baseline and follow-up(s). When required data were not available in the publication, emails were sent to the author for correspondence of identified studies, to request the missing data.

Methodological quality within studies was determined using Cochrane Collaboration's Risk of Bias tool that focused on following domains: (i) sequence generation, (ii) allocation concealment, (iii) blinding of participants, (iv) blinding of personnel and outcome assessors and (v) selective outcome reporting (27). Judgements of low ('+'), unclear ('?') or high risk of bias ('-') were made according to criteria specified by Cochrane and summarised with domains symbol-coded.

2.4.2 Data synthesis

For continuous outcomes, mean change data with SDs were extracted or, if unavailable, calculated from baseline and end of intervention (EOI) values for each group. Missing SDs were either: (i) calculated from standard error of mean or 95% CI, if available, or (ii) imputed

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using a SD from a trial of similar length and intervention as judged by the review author (30). A full-text article could not be obtained for the trial by Kandel (35) and only baseline and EOI means were reported in the abstract. Number of participants at EOI was estimated using the mean attrition rate of all other included trials with similar exercise interventions. SDs were imputed from another trial (28) judged to be similar in terms of population group and length of intervention. Where possible data were combined using meta-analysis to generate a mean difference (MD) or standardised mean difference (SMD). SMD was used for analyses of ordinal data (PA level), and continuous data (FFM and limb strength) when the same outcomes were measured using different instruments, scales or body parts.

Four of nine studies included in the quantitative analyses presented data at multiple time points during the trial or beyond the EOI. For comparisons, meta-analyses were conducted on data collected at the EOI only. Data on dichotomous outcomes were extracted and combined using meta-analysis to generate relative risks. Though two studies measured and reported balance, they were not comparable as different types of data were used (52, 54).

All analyses were carried out in Review Manager (RevMan) 5.3 using a fixed-effect meta-analysis. A P value of ≤0.05 was considered statistically significant. Overall heterogeneity was assessed by measuring inconsistency (I^2) based on chi-squared test. The following classification of heterogeneity was used: I^2 ≤50%: *low*, I^2 >50 to <75%: *moderate*, and I^2 ≥75%: *considerable* based on Cochrane's rough guide to interpretation of I^2 (30). For studies where missing data could not be obtained, results were summarised in narrative.

The main results of the review were displayed in a summary of findings table. For each primary outcome measure: a brief description of included studies (number of trials and participants, and mean follow-up); the quality of evidence; and SMD/MD (95% CI) of nutrition and exercise vs. nutrition interventions, were presented. Quality of the studies were judged by the review author using Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group (3) as specified by Cochrane. Limitations of study design, indirectness of results, unexplained heterogeneity or inconsistent results, imprecision of results and publication bias were factors that lower the quality level of evidence. After consideration of study type and these factors the review author deemed evidence as 'high', 'moderate', 'low' or 'very low' quality and gave brief reasons within the table.

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3. Results

3.1 Study characteristics

Eleven RCTs comprising 1,459 participants were identified for inclusion in the systematic review. **Figure 1** displays the results of the search and study selection process. Full-texts were obtained for ten trials from which detailed study characteristics were retrieved (**Table 1**). Only the abstract was available for the remaining study and contained limited data and trial information (35). Of the included studies participants were: aged sixty-five or over; female dominant (range: 60-100% of sample populations); defined as frail, sarcopenic, undernourished or at risk of malnutrition indicated by BMI cut-offs and amounts of weight loss, and/or reduced mobility; and the majority were community-based. Three trials were conducted in an acute setting: the trial by Blanc-Bisson (6) was conducted on acutely ill, bedridden or reduced mobility patients in hospital; Miller (43) included participants from a hospital setting following a lower limb fracture; and Kandel's (35) population group was selected from a tertiary care centre in India.

Exercise and nutrition interventions were diverse. The majority of studies focused on high intensity and/or progressive resistance sessions whilst others incorporated Nordic walking (35) or intensive physiotherapy rehabilitation (6) as the exercise component of the intervention. Oral nutritional supplements were the most popular approach to nutritional support with some trials focusing on single macronutrients (37,38) or micronutrients only (50). Additionally, length of intervention varied across trials: the majority were three months, the shortest was 12.6 (± SD 6.4) days (6) and the longest was nine months (8).

3.2 Risk of bias assessment

Overall methodological quality of included studies ranged from low to adequate (**Table 2**). Due to the nature of exercise interventions and the impossibility of blinding participants to these, all studies were judged to be at high risk of performance bias. Although some trials attempted to reduce performance bias by blinding or double blinding the nutrition intervention (6, 8, 20, 28, 49). Two studies were judged to be low risk of selection, detection, attrition and reporting biases and therefore suggested good methodological quality (37, 38). Many studies failed to address selection bias: five did not use a random allocation sequence and five did not provide sufficient information on allocation sequence in their methodology to permit judgement.

3.3 Primary outcomes

Data were available for quantitative analysis from nine included studies. (**Table 3**). There were no statistically significant differences in FFM (five studies; SMD -0.05; 95% CI -0.27 to 0.18; P = 0.70), PA level (three studies; SMD 0.04; 95% CI -0.26 to 0.33; P = 0.81) and timed up-and-go test (two studies; MD -0.80; 95% CI -2.06 to 0.47; P = 0.22) between the participants who received either nutrition and exercise or nutrition intervention alone. No heterogeneity was observed for FFM (I^2 = 0%; P = 0.53), PA level (I^2 = 0%; P = 0.99) and low heterogeneity was observed for timed up-and-go test (I^2 = 32%; P = 0.23).

Data on muscle strength, including handgrip and limb strength, were available from eight studies and were analysed both separately and in a combined analysis (**Figure 2**). Subgroup analysis of data from two studies of handgrip strength showed there was no statistically significant difference in handgrip strength between participants who either received nutrition and exercise or nutrition intervention alone (SMD 0.22; 95% CI -0.14 to 0.58; P = 0.23), low heterogeneity was observed (I^2 = 31%; P = 0.23). Subgroup analysis of data from six studies on limb strength showed that participants who received nutrition and exercise had greater limb strength than those who received nutrition intervention alone (SMD 0.33; 95% CI 0.13 to 0.53; P = 0.001), low heterogeneity was observed (I^2 = 40%; P = 0.14). Combined analysis of data from all studies showed participants who received nutrition and

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exercise had greater muscle strength than those who received nutrition intervention alone (SMD 0.30; 95% CI 0.13 to 0.48; P = 0.0008), low heterogeneity was observed (I^2 = 30%; P = 0.19).

Data on gait speed were available from seven studies (**Figure 3**). Participants receiving nutrition intervention alone had faster gait speeds than those receiving nutrition and exercise (SMD 0.38; 95% CI 0.19 to 0.56; P < 0.0001), low heterogeneity was observed (I^2 = 35%; P = 0.16).

Three studies did not have data available for quantitative analysis. Blanc-Bisson (6) reported factor analyses of baseline data but not raw outcome data. Although some results were reported in narrative. The intensive physiotherapy rehabilitation and nutritional supplement had no significant additional effect on handgrip strength, ADL, and 'other anthropometric measures' (p. 397); assumed to include skinfold thickness and limb circumference, compared to usual physiotherapy care and nutritional supplement. Bonnefoy et al (8) analysed data from four groups: (i) nutritional supplement plus control activity, (ii) supplement plus exercise, (iii) placebo plus exercise and (iv) placebo plus control activity, in a factorial design trial comparing exercise with control and supplements with placebo. Though de Jong (20) reported data on FFM, like Bonnefoy (8), all other outcome data were reported in factorial analyses. Email requests for the required data were sent but no response received.

3.4 Secondary outcomes

There was no statistically significant difference in hospitalisation (two studies; relative risk 0.73; 95% CI 0.15 to 3.53; P = 70) between the participants who received either nutrition and exercise or nutrition intervention alone. No heterogeneity was observed for hospitalisation (I^2 = 0%; P = 0.54).

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4. Discussion

The aim of this systematic review was to assess whether exercise provides additional benefits when combined with nutritional support on physical functioning, QOL, nutritional status, morbidity and mortality in nutritionally vulnerable older adults. Findings indicate very low quality evidence that a combined intervention leads to greater improvements in muscle strength (**Figure 2**) and low quality evidence of a lack of effect on mobility, functional independence, lean body mass and morbidity compared to nutritional support alone (**Table 3**). Moderate quality evidence from two studies suggested no benefits of combined intervention on handgrip strength. Unexpectedly, the combined intervention led to reduced mobility with slower gait speeds than nutritional support alone (**Figure 3**). No studies reported mortality and only one measured QOL and as such these outcomes were not assessed.

The effects of exercise combined with nutritional support on muscle strength seen in this review are similar to high quality evidence from a Cochrane review that assessed the effects of progressive resistance training without nutritional supplementation on functional status in older adults (41). They also found positive effects on muscle strength (73 RCTs; SMD 0.84; 95% CI 0.67 to 1.00), as well as improved physical ability (22 RCTs; SMD 0.14; 95% CI 0.05 to 0.22), gait speed (24 RCTs; MD 0.8 m/s; 95% CI 0.04 to 0.12) and getting out of a chair (11 RCTs; SMD -0.94; 95% CI -1.49 to -0.38). The findings of this review contrast with those of Lui *et al* in not finding improvements in functional measures other than muscle strength. This could be due to the limited number of studies identified (n= 11, compared with n= 121 in the Cochrane review) and heterogeneous interventions. There was considerable heterogeneity in the types and intensity of both interventions between studies. Specifically, exercise interventions used in studies varied from high intensity resistance exercise in some

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studies, moderate intensity exercise individualized to participants ability, Nordic walking and a physiotherapy programme in hospitalized patients. In addition, studies used different inclusion criteria to identify a nutritionally frail population. Diverse and heterogeneous populations and interventions as well as variations in reporting of outcomes may explain some of the inconsistent effects. The findings on the potentially beneficial effects on limb strength should be considered together with the quality of evidence. There was only very low quality evidence of a positive effect on limb strength. All studies were small in size and only one study (37) was at an overall low risk of bias. The remaining studies were at high or unclear risk of bias for one or more elements and their findings should be viewed with an appropriate level of caution. Whilst it is tempting to focus on the statistically significant findings of any investigation, it should be noted that the higher quality evidence was for handgrip strength which showed no difference between groups, although data were available from only few small studies.

Furthermore this review did not investigate the effects of exercise alone compared with ONS combined with exercise, making it difficult to establish whether nutritional support enhances the benefits of exercise on muscle strength. In addition, the Cochrane review included both healthy *and* frail older adults, whereas this review focused only on frail undernourished adults, who were more likely to require nutritional support and may have been less able to exercise.

The positive effect of nutritional support on gait speed is supported by a RCT which found protein-energy supplementation significantly reduced decline in gait speed versus controls in frail older adults (36). This suggests the importance of nutrition intervention in slowing age-related functional decline. The unexpected finding was that exercise combined with nutritional intervention did not further improve gait speed. Many studies contradict this finding. A systematic review (42) and three later RCTs (16, 29, 61) showed exercise improved gait speed among older populations. All but one of these studies (29) included healthy older adults. Dietary provision for undernourished participants in the present review may have been inadequate to meet increased nutritional requirements resulting from greater energy expenditure in the combined nutrition and exercise groups. Evidently only one RCT tailored nutritional support to each participant (55). Thus suboptimal nutritional support may explain why findings failed to show added benefits of exercise with nutritional support on mobility.

Additionally, neglecting to individualise nutritional support may have contributed to the lack of effect of either intervention on other measures of physical functioning and nutritional status. Nutritional interventions targeted at older adults can prevent muscle decline provided intake of protein is adequate (25). Protein requirements are based on provisions required for nitrogen balance (63). Metabolic studies conducted by Campbell (10) found current recommendations for protein intake appear to be insufficient to maintain this balance in older adults. Therefore higher than recommended protein intakes are likely to be required for physical functioning on top of nitrogen balance (7). As the majority of included studies provided supplements without full nutritional assessment and, where reported, compliance varied from 54 to 99%; it cannot be assumed dietary requirements were met. This may be the reason no positive effect was observed on lean body mass.

Research suggests timing of supplement delivery is an important consideration for maintaining or increasing FFM in nutrition and exercise interventions. Consuming supplements in close proximity to exercise appears to enhance exercise-induced effects on muscle mass (11, 18, 24). Yet only one study in this review considered timing of supplementation. Participants received supplements within five minutes post-exercise, but the timed intervention did not influence lean body mass (14). Other RCTs have also demonstrated timing of nutritional supplement does not augment the effect of exercise on muscle mass in the elderly (12, 13, 22). Although, these trials were conducted on healthy elderly populations, the majority of which were men. Participants in the present review were nutritionally vulnerable older adults and the majority were women, hence reducing the comparability of findings from the RCTs to this population group.

Precautions were taken to minimise reporting bias in the review process. A protocol was completed, the review was registered, multiple databases were searched and no time or language restrictions were implemented in the search strategy. However, unpublished trials were not sought after, there was no independent screening of titles and abstracts during the study selection stage although the same search was undertaken by two previous students and it was possible to compare the studies identified for this review with those identified previously which strengthens this aspect of the review. Reporting bias could not be assessed using a funnel plot due to limited number of studies available for quantitative analysis. Furthermore, even though Kim 's two trials (37, 38) used the same target population, they were included in the review as two separate studies due to different participant criteria and nutritional interventions. Therefore, multiple publication bias may have overestimated effects of dual-intervention on outcome measures when both studies were included. Due to restricted time and resources and the unavoidable publication bias of positive significant findings across literature, reporting bias was inevitable and limits findings of the present review. Another limitation was small sample sizes from studies, ranging from thirteen to forty-nine limiting generalisability of findings to wider frail elderly populations.

The importance of PA and nutritional support for the wellbeing of older populations is highlighted by national guidelines. British Association for Parenteral and Enteral Nutrition's (BAPEN's) toolkit for the provision of nutritional care (9) recognises National Institute for Health and Care Excellence (NICE) guidelines on malnutrition (47) as 'good nutritional care'. In addition, BAPEN (9) identifies a vicious cycle of fatigue and inactivity related to malnutrition causing reduced muscle strength, leading to reduced ability to shop and cook, exacerbating a

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malnourished state. Regardless, NICE (47) has not incorporated PA into recommendations for nutritional support in adults. Although different NICE guidelines on mental wellbeing for over sixty-five's (48) recommend 'strength and resistance exercise, especially for frail older people'. Despite the role of nutrition and exercise on the functionality of frail older adults, they are addressed separately in national recommendations without guidance for integration. The lack of detail surrounding optimal approach and monitoring of dual-intervention has likely contributed to clinical heterogeneity of research in this area.

In summary, there is limited very low quality evidence from RCTs that exercise provides additional improvements to muscle strength alongside nutritional support in nutritionally vulnerable older adults. The effects on other measures of functional status, QOL, nutritional status, morbidity and mortality remain unclear due to a small number of inadequately powered studies. Further research is warranted surrounding optimal exercise intervention and individualisation and timing of nutritional supplements in relation to exercise on the functional and nutritional status in frail, undernourished older adults. More emphasis should be placed on the tools used to define nutritional status at inclusion in future trials as consensus moves towards the importance of function as an important element of nutritional vulnerability (15). Recommendations combining nutrition and exercise interventions for this population group may then be developed in light of research findings.

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Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Statement of authorship

Design and supervision of the research; CB. Conduct of the research, analysis and interpretation of data; JW. Writing the manuscript and primary responsibility for final content; JW. Both authors participated in editing and final revisions of the manuscript. Reading and approval of the final manuscript; CB.

Conflict of Interest Statement

Authors have no conflicts of interest to declare.

Acknowledgements

None

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References

1. Alemán-Mateo H, Macías L, Esparza-Romero J, Astiazaran-García H, Blancas AL. Physiological effects beyond the significant gain in muscle mass in sarcopenic elderly men: evidence from a randomized clinical trial using a protein-rich food. Clin Interventions Aging 2012;7:225.
2. Ali S, Garcia JM. Sarcopenia, cachexia and aging: diagnosis, mechanisms and therapeutic options-a mini-review. Gerontology 2014;60(4):294-305.
3. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64(4):401-406.
4. Baumgartner RN. Body composition in healthy aging. Ann N Y Acad Sci 2000;904(1):437-448.
5. Beck AM, Ovesen L. At which body mass index and degree of weight loss should hospitalized elderly patients be considered at nutritional risk. Clin Nutr 1998;17(5):195-198.
6. Blanc-Bisson C, Dechamps A, Gouspillou G, Dehail P, Bourdel-Marchasson I. A randomized controlled trial on early physiotherapy intervention versus usual care in acute care unit for elderly: potential benefits in the light of dietary intakes. J Nutr Health Aging 2008;12(6):395-399.
7. Bohé J, Low A, Wolfe RR, Rennie MJ. Human muscle protein synthesis is modulated by extracellular, not intramuscular amino acid availability: a dose-response study. J Physiol 2003;552(1):315-324.
8. Bonnefoy M, Cornu C, Normand S, Boutitie F, Bugnard F, Rahmani A, Lacour JR, Laville M. The effects of exercise and protein–energy supplements on body composition and muscle function in frail elderly individuals: a long-term controlled randomised study. Br J Nutr 2003;89(5):731-738.
9. Brotherton A, Simmonds N, Stroud M. Meeting quality standards in Nutriitonal Care: a toolkit for commissioners and providers in England. British Association for Parenteral and Enteral Nutriiton (BAPEN); 2012
10. Campbell WW, Crim MC, Dallal GE, Young VR, Evans WJ. Increased protein requirements in elderly people: new data and retrospective reassessments. Am J Clin Nutr 1994;60(4):501-509.
11. Candow DG, Chilibeck PD. Timing of creatine or protein supplementation and resistance training

ACCEPTED MANUSCRIPT

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in the elderly. Appl Physiol Nutr and Metab 2007;33(1):184-190.

12. Candow DG, Chilibeck PD, Facci M, Abeysekara S, Zello GA. Protein supplementation before and after resistance training in older men. Eur J Appl Physiol 2006;97(5):548-556.

13. Candow DG, Zello GA, Ling B, Farthing JP, Chilibeck PD, McLeod K, Harris J, Johnson S. Comparison of creatine supplementation before versus after supervised resistance training in healthy older adults. Res Sports Med 2014;22(1):61-74.

14. Carlsson M, Littbrand H, Gustafson Y, Lundin-Olsson L, Lindelöf N, Rosendahl E, Håglin L. Effects of high-intensity exercise and protein supplement on muscle mass in ADL dependent older people with and without malnutrition—A randomized controlled trial. J Nutr Health Aging 2011;15(7):554-560.

15. Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, Muscaritoli M, Nyulasi I, Ockenga J, Schneider SM. Diagnostic criteria for malnutrition–an ESPEN consensus statement. Clin Nutr 2015;34(3):335-340.

16. Chmelo EA, Crotts CI, Newman JC, Brinkley TE, Lyles MF, Leng X, Marsh AP, Nicklas BJ. Heterogeneity of physical function responses to exercise training in older adults. J Am Geriatr Soc 2015;63(3):462-469.

17. Cochrane Public Health Group(CPHG). Guide for Developing a Cochrane Protocol. 2011 Available at: www.ph.cochrane.org

18. Cribb PJ, Hayes A. Effects of supplement-timing and resistance exercise on skeletal muscle hypertrophy. Med Sci Sports Exerc 2006;38(11):1918-1925.

19. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel J-P, Rolland Y, Schneider SM. Sarcopenia: European consensus on definition and diagnosis. Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39(4):412-423.

20. De Jong N, Chin A Paw MJM, De Groot LC, Hiddink GJ, Van Staveren WA. Dietary supplements and physical exercise affecting bone and body composition in frail elderly persons. Am J Public Health 2000;90(6):947.

21. Degens H, Korhonen MT. Factors contributing to the variability in muscle ageing. Maturitas. 2012;73(3):197-201.
22. Dideriksen KJ, Reitelseder S, Petersen SG, Hjort M, Helmark IC, Kjær M, Holm L. Stimulation of muscle protein synthesis by whey and caseinate ingestion after resistance exercise in elderly individuals. Scand J Med Sci Sports 2011;21(6)
23. Dillon EL, Sheffield-Moore M, Paddon-Jones D, Gilkison C, Sanford AP, Casperson SL, Jiang J, Chinkes DL, Urban RJ. Amino acid supplementation increases lean body mass, basal muscle protein synthesis, and insulin-like growth factor-I expression in older women. J Clin Endocrinol Metab 2009;94(5):1630-1637.
24. Esmarck B, Andersen JL, Olsen S, Richter EA, Mizuno M, Kjær M. Timing of postexercise protein intake is important for muscle hypertrophy with resistance training in elderly humans. The J Physiol 2001;535(1):301-311.
25. Evans WJ. Protein nutrition, exercise and aging. J Am Coll Nutr 2004;23(sup6):601S-609S.
26. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, Jatoi A, Loprinzi C, MacDonald N, Mantovani G. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011;12(5):489-495.
27. Ferrando AA, Paddon-Jones D, Hays NP, Kortebein P, Ronsen O, Williams RH, McComb A, Symons TB, Wolfe RR, Evans W. EAA supplementation to increase nitrogen intake improves muscle function during bed rest in the elderly. Clin Nutr 2010;29(1):18-23.
28. Fiatarone MA, O'Neill EF, Ryan ND, Clements KM, Solares GR, Nelson ME, Roberts SB, Kehayias JJ, Lipsitz LA, Evans WJ. Exercise training and nutritional supplementation for physical frailty in very elderly people. New Eng J Med 1994;330(25):1769-1775.
29. Giné-Garriga M, Guerra M, Pagès E, Manini TM, Jiménez R, Unnithan VB. The effect of functional circuit training on physical frailty in frail older adults: a randomized controlled trial. J Aging Phys Act 2010;18(4):401-424.
30. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. John Wiley & Sons; 2011
ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

31. Houston DK, Nicklas BJ, Ding J, Harris TB, Tylavsky FA, Newman AB, Lee JS, Sahyoun NR, Visser M, Kritchevsky SB. Dietary protein intake is associated with lean mass change in older, community-dwelling adults: the Health, Aging, and Body Composition (Health ABC) Study. Am J Clin Nutr 2008;87(1):150-155.

32. Janssen I, Heymsfield SB, Wang ZM, Ross R. Skeletal muscle mass and distribution in 468 men and women aged 18-88 yr. J Appl Physiol (1985). 2000;89(1):81-88.

33. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. J Am Geriatr Soc 2002;50(5):889-896.

34. Janssen I, Shepard DS, Katzmarzyk PT, Roubenoff R. The healthcare costs of sarcopenia in the United States. J Am Geriatr Soc 2004;52(1):80-85.

35. Kandel R, Chatterjee P, Kumar V, Gopalan V, Ambashtha, A, Jathar S, Dey AB. Impact of nutritional supplementation and Nordic walking in frail older patients in geriatrics department of tertiary care hospital in India. Eur Geriatr Med 2014;5:S127-128 (Abstract).

36. Kim C-O, Lee K-R. Preventive effect of protein-energy supplementation on the functional decline of frail older adults with low socioeconomic status: a community-based randomized controlled study. J Gerontol A Biol Sci Med Sci 2012;68(3):309-316.

37. Kim HK, Suzuki T, Saito K, Yoshida H, Kobayashi H, Kato H, Katayama M. Effects of exercise and amino acid supplementation on body composition and physical function in community-dwelling elderly Japanese sarcopenic women: a randomized controlled trial. J Am Geriatr Soc 2012;60(1):16-23.

38. Kim H, Suzuki T, Kim M, Kojima N, Ota N, Shimotoyodome A, Hase T, Hosoi E, Yoshida H. Effects of exercise and milk fat globule membrane (MFGM) supplementation on body composition, physical function, and hematological parameters in community-dwelling frail Japanese women: a randomized double blind, placebo-controlled, follow-up trial. PloS one. 2015;10(2):e0116256.

39. Konishi M, Ishida J, Haehling S, Anker SD, Springer J. Nutrition in cachexia: from bench to

ACCEPTED MANUSCRIPT

bedside. J Cachexia Sarcopenia Muscle. 2016;7(2):107-109.

40. Lammes E, Rydwik E, Akner G. Effects of a nutritional intervention and physical training on energy intake, resting metabolic rate and body composition in frail elderly. A randomised controlled pilot study. J Nutr Health Aging 2012;16(2):162-167.

41. Liu C, Latham NK. Progressive resistance strength training for improving physical function in older adults. Cochrane Database Syst Rev 2009; Jul8(3):CD002759. doi: 10.1002/14651858.CD002759.pub2

42. Lopopolo RB, Greco M, Sullivan D, Craik RL, Mangione KK. Effect of therapeutic exercise on gait speed in community-dwelling elderly people: a meta-analysis. Phys Ther 2006;86(4):520-540.

43. Miller MD, Crotty M, Whitehead C, Bannerman E, Daniels LA. Nutritional supplementation and resistance training in nutritionally at risk older adults following lower limb fracture: a randomized controlled trial. Clin Rehabil 2006;20(4):311-323.

44. Milne AC, Potter J, Avenell A. Protein and energy supplementation in elderly people at risk from malnutrition. Cochrane Database Syst Rev 2005;Apr 18(2): CD003288.

45. Morley JE. Decreased food intake with aging. J Gerontol A Biol Sci Med Sci 2001;56(suppl_2):81-88.

46. Munk T, Tolstrup U, Beck AM, Holst M, Rasmussen HH, Hovhannisyan K, Thomsen T. Individualised dietary counselling for nutritionally at-risk older patients following discharge from acute hospital to home: a systematic review and meta-analysis. J Hum Nutr Diet 2016;29(2):196-208.

47. National Collaborating Centre for Acute Care (UK). Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition CG32. 2006. Available at: http://guidance.nice.org.uk/CG32/niceguidance/pdf

48. National Collaborating Centre for Acute Care (UK). Mental wellbeing in over 65s: occupational therapy and physical activity interventions, PH16. 2008. Available at: http://guidance.nice.org.uk/PH16/niceguidance/pdf

49. Ng TP, Feng L, Nyunt MSZ, Feng L, Niti M, Tan BY, Chan G, Khoo SA, Chan SM, Yap P. Nutritional, physical, cognitive, and combination interventions and frailty reversal among older adults: a randomized controlled trial. Am J Med 2015;128(11):1225-1236. e1.

50. Paw Chin A MJM, de Jong N, Schouten EG, Hiddink GJ, Kok FJ. Physical exercise and/or enriched foods for functional improvement in frail, independently living elderly: a randomized controlled trial. Arch Phys Med Rehabil 2001;82(6):811-817.

51. Paw Chin A MJM, De Jong N, Schouten EG, Van Staveren WA, Kok FJ. Physical exercise or micronutrient supplementation for the wellbeing of the frail elderly? A randomised controlled trial. Br J Sports Med 2002;36(2):126-131.

52. PROSPERO. International prospective register of systematic reviews. NHS National Institute for Health Research. 2015. Available from: http://www.crd.york.ac.uk/PROSPERO

53. Rosendahl E, Lindelöf N, Littbrand H, Yifter-Lindgren E, Lundin-Olsson L, Håglin L, Gustafson Y, Nyberg L. High-intensity functional exercise program and proteinenriched energy supplement for older persons dependent in activities of daily living: a randomised controlled trial. Aust J Physiother 2006;52(2):105-113.

54. Russell CA, Elia M. Nutrition Screening Survey in the UK and Republic of Ireland in 2011. 2012 A Report by the Malnutrition Advisory Group of the British Association for Parenteral and Enteral Nutrition (BAPEN). Available from: http://www.bapen.org.uk/pdfs/nsw/nsw-2011-report.pdf

55. Rydwik E, Lammes E, Frändin K, Akner G. Effects of a physical and nutritional intervention program for frail elderly people over age 75. A randomized controlled pilot treatment trial. Aging Clin Exp Res 2008;20(2):159-170.

56. Rydwik E, Frändin K, Akner G. Effects of a physical training and nutritional intervention program in frail elderly people regarding habitual physical activity level and activities of daily living - a randomised controlled pilot study. Arch Gerontol Geratr 2010;51(3):282-289.

57. Scognamiglio R, Avogaro A, Negu C, Piccolotto R, de Kreutzenberg SV, Tiengo A. The effects of oral amino acid intake on ambulatory capacity in elderly subjects. Aging Clin Exp Res 2004;16:443-447.

58. Solerte SB, Gazzaruso C, Bonacasa R, Rondanelli M, Zamboni M, Basso C, Locatelli E, Schifino N, Giustina A, Fioravanti M. Nutritional supplements with oral amino acid mixtures increases whole-body lean mass and insulin sensitivity in elderly subjects with sarcopenia. Am J Cardiol 2008;101(11):S69-S77.

59. Suetta C, Andersen JL, Dalgas U, Berget J, Koskinen S, Aagaard P, Magnusson SP, Kjaer M. Resistance training induces qualitative changes in muscle morphology, muscle architecture, and muscle function in elderly postoperative patients. J Appl Physiol 2008;105(1):180-186.

60. Vasquez-Morales A, Wanden-Berghe C, Sanz-Valero J. Exercise and nutritional supplements; effects of combined use in people over 65 years; a systematic review. Nutr Hosp 2012;28(4):1077-1084.

61. Wang R-Y, Wang Y-L, Cheng F-Y, Chao Y-H, Chen C-L, Yang Y-R. Effects of combined exercise on gait variability in community-dwelling older adults. Age 2015;37(3):40.

62. WHO EC. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363(9403):157-163.

63. Wolfe RR. The underappreciated role of muscle in health and disease. Am J Clin Nutr 2006;84(3):475-482.

64. Xu Z-r, Tan Z-j, Zhang Q, Gui Q-f, Yang Y-m. Clinical effectiveness of protein and amino acid supplementation on building muscle mass in elderly people: a meta-analysis. PloS one. 2014;9:e109141.

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Table 1: Characteristics of included studies

Study ID	Total number of participants	Population description	Inclusion criteria	Study methods	Intervention description	Comparison	Frequency & duration	Follow-up	Outcomes[a]
Blanc-Bisson 2008 (6)	76	Hospitalized patients recruited within 1 d of admission to an acute-care geriatric medicine unit. France. 72% female.	(1) Aged >70, & (2) confined to bed or walking from bed to chair with human assistance.	Prospective, 2-arm RCT: (1) intensive physiotherapy rehabilitation, and (2) usual care.	Physiotherapy: Usual care plus physiotherapy program started d 1-2 (working on triceps, legs & pelvis.	Usual care: transferred from bed to chair as soon as possible & starting to walk from d 3-6. Plus hospital diet (1800-2000 kcal/d) and 1 ONS (200 kcal, 15 g protein).	Usual care: from d 3-6 3 sessions/ wk until discharge. Physiotherapy: 30 mins twice daily 5 x/ wk until clinically stable then usual care.	When patients clinically stable and 1 mo later.	Body weight, BMI, **calf and arm circumference**, **triceps SFT**, energy and protein intakes, serum albumin, CRP, **ADL** and **handgrip strength** Ax at baseline, & when clinically stable and/or after 1 mo.
Bonnefoy 2003(8)	57	Frail elderly from 16 retirement homes, France; 88% female.	(1) Aged >72, & (2) frail.	4-arm RCT: (1) supplement & memory, (2) supplement & exercise, (3) placebo & exercise, & (4) placebo & memory.	ONS: 200 ml (200 kcal, 25 g carbohydrate, 15 g protein and 4.4 g fat plus 50% RDA for vitamins and minerals). Exercise: moderate, intensity progressive strengthening, balance	Placebo: drink containing no energy, protein, vitamins or minerals. Memory: memory sessions 3 x/ wk.	ONS: 2 x/ day for 9 mo. Exercise: 60 mins 3 x/ wk for 9 mo.	EOI.	**Chair-stand test** and **RMR** baseline and EOI. **FFM**, **muscle power**, **walking test**, stair climbing and BMI at baseline, 3 mo and EOI.

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					training and flexibility exercises.				
Paw 2001 (50), Paw 2002 (51) de Jong, 2000a (20)	217	Free-living frail elderly. The Netherlands ; 72% female.	(1) Aged ≥70 (2) required health care, (3) inactivity, (4) BMI ≤20 kg/m^2, (5) no multivitamin supplements, &(6)understan d study procedures.	4-arm RCT: (1) control, (2) nutrition, (3) exercise, & (4) nutrition & exercise.	Nutrition: micronutrient-dense, fruit-based products & dairy products (115 kcal;met 100% Dutch RDA for vitamins plus 25-100% RDA for minerals). Exercise: group sessions on maintenance/ improvement of mobility &performance of ADL..	Control: regular food product (115 kcal; not fortified) & social programme consisting of 1 x 90 min session every 2 wks.	Nutrition: consumption of 1 fruit-based & 1 dairy product/ day for 17 wks. Exercise: 45 mins 2 x/ wk for 17 wks.	EOI.	Body weight, BMI, **FFM**, fat mass, WC, HC, WHR, bone mass, BMD and bone calcium, **functional capacity** (. **balance**, **gait speed**, **chair-stand test**), **physical fitness ADL**, **PA** and **wellbeing** at baseline & EOI.
Fiatarone 1994 (28)	100	Frail nursing home residents, USA; 63% female.	(1) Aged ≥70, & (2) able to walk 6 m.	4-arm RCT: (1) training, (2) ONS, (3) training & ONS & (4) control.	Training: high intensity progressive resistance training. ONS: 240 ml (360 kcal: 60% CHO, 23% fat, 17% protein, ⅓ RDA vitamins & minerals).	Placebo activities: 3 recreational activities. Placebo drink: 240 ml (4 kcal)..	Training: 45 mins 3 x/ wk for 10 wks. ONS: 1 x/ day for 10 wks.	EOI.	**Muscle strength**, **gait speed**, stair-climbing power, **PA level**, **mid-thigh circumference**, **thigh muscle area**, body weight, **FFM** and energy intakeat baseline and EOI.
Kandel	90	Frail older	(1) Aged ≥70,	3-arm RCT:	Diet: ONS.	Control:	ONS: 8 wks.	EOI.	**Gait speed**,

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2014 (35)[b]		patients in geriatrics department of tertiary care hospital, India.	& (2) frail.	(1) diet, (2) diet & exercise, & (3) control.	Exercise: Nordic walking training.	dietary counselling.	Exercise: 30 mins 5 x/ wk for 8 wks. Control: 8 wks.		**grip strength** and **frailty score** at baseline and EOI.
Kim 2012 (37)	155	Sarcopenic elderly people from an urban community , Japan; 100% female.	(1) Aged ≥75, & (2) 1 or more of: (i) appendicular skeletal muscle mass/ ht^2 <6.42 kg/m^2 & knee extension strength <1.01 Nm/kg, (ii) appendicular skeletal muscle mass/ ht^2 <6.42 kg/m^2 & usual walking speed <1.22 m/s, (iii) BMI <22 kg/m^2 & knee extension strength <1.01 Nm/kg, & (iv) BMI <22 kg/m^2 & usual walking speed <1.22 m/s.	4-arm RCT: (1) exercise & ONS, (2) exercise, (3) ONSt, & (4) health education.	Exercise: warm up, strength, balance, gait training & cool down plus progressive resistance.. ONS: 3 g leucine-rich amino acid powders taken with water/ milk.	Health education: 3 classes 1x mo for 3 mo.	Exercise: 60 mins 2 x/ wk for 3 mo. Supplement: 3 g amino acid mixture 2 x/ day for 3 mo.	EOI.	BMI, **FFM**, usual & maximal **walking speeds** & **knee extension strength** at baseline & EOI.
Kim, 2015(38)	131	Frail elderly people from an urban community, Japan;	(1) Aged ≥75, & (2) 3 or more of: (i) wt loss >2-3 kg in 6 mo, (ii)	4-arm RCT: (1) exercise & ONS, (2) exercise & placebo, (3)	Exercise: warm up, strength, balance, gait training & cool	Placebo: 6 x whole milk powder tablets 1 x/ day.	Exercise: 60 mins 2 x/ wk for 3 mo. ONS: 6 MFGM tablets 1 x/ day	EOI and 7 mo.	Frailty, BMI, **FFM**, **leg muscle mass**, BMD, fat mass, **handgrip**

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		100% female.	weakness: grip strength <19 kg, (iii) slow walking speed: <1.0 m/s, (iv) exhaustion, & (v) low activity.	ONS, & (4) placebo.	down plusrogressive resistance. Supplement: 1 g MFGM.		for 3 mo.		**strength**, **knee extension strength**, **walking speed**, **TUG test**, serum brain-derived neurotrophic factor, serum insulin-like growth factor-1 (IGF-1), serum IGF-1 binding protein, serum myostatin &growth hormone at baseline, EOI & 7 mo.
Miller 2006(43)	100	Nutritionally at-risk older adults hospitalised, following a fall-related lower limb fracture, Australia; 79% female.	(1) Aged ≥70, (2) Fall-related lower limb fracture, , (3) Comprehend instructions, (5) fully bear weight on side of injury post 7 days, (6) malnourished: <25th percentile for MUAC, & (7) independently mobile pre-fracture.	4-arm RCT: (1) ONS, (2) training, (3) ONS & training, & (4) control.	Training: progressive resistant training,. ONS: *Fortisip* (1.5 kcal/ml: 49% carbohydrate, 35% fat and 16% protein) meets 45% of individual estimated energy requirements.	Control: general information on diet & exercise. 3 x/ wk for weeks 1-6 then 1 x/ wk for weeks 7-12.	Training: 20-30 min sessions 3 x/ wk for 3 mo. ONS: 4 x doses of equal volume /day.	EOI.	Body weight weekly. **Gait speed** at EOI. **Quadricep strength**, **QOL** and **hospitalisation** at baseline and EOI.
Ng 2015 (49)	246	Community-living pre-frail & frail	(1) Aged ≥65, (2) independently	5-arm RCT: (1) ONS, (2) cognitive	Physical training: moderate,	Control: access to one	Physical training: 90 mins 2 x/ wk for 3 mo then 3	EOI & 12 mo.	Frailty score, reduction in frailty, BMI,

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		older adults. Singapore; 61% female.	mobile, (3) living at home, &(4) pre-frail or frail using physical frailty criteria.	training, (3) physical training, (4) ONS & cognitive & physical training, & (5) control.	progressive intensity exercise sessions. ONS: (1) *Fortisip Multi Fibre* plus (2) iron & folate, (3) vitamin B_6 & B_{12}, & (4) calcium & vitamin D supplements. Cognitive training..	standard care health & aged care services & received placebo drink&tablets 1 x/ day for 6 mo.	mo of home-based exercises. ONS: taken 1 x/ day for 6 mo. Cognitive training: 2 hr sessions 1 x/ wk for 3 mo then 2 hr sessions 1 x/ fortnight for 3 mo.		**knee extension**, **gait speed**, **energy score**, **dependency**, **hospitalisation** & falls at baseline, 3 mo, EOI & 12 mo.
Rosendahl 2006 (53)& Carlsson 2011 (14)	191	Residents at 9 care facilities, Sweden; 73% female.	(1) Aged ≥65, (2) dependent for ADL, (3) able to stand from chair with armrests with help from no more than one person, & (4) MMSE score ≥10.	RCT : (1) exercise & ONS, (2) exercise & placebo, (3) control & ONS, & (4) control & placebo.	Exercise: High- intensity functional exercises. ONS: Protein-enriched energy 200ml (98 kcal, 7.4 g protein, 15.7 g CHO per 100g).	Control activities involved sitting. 200ml placebo (47 kcal, 0.2 g protein, 10.8 g CHO per 100g).	Frequency of exercise sessions varied based on individual recommendations. 45 min each over 3 mo. ONS offered 5 mins after exercise .	EOI & 6 mo.	**Balance score**, **gait speed**, **lower-limb strength**, **FFM** and body weight at baseline, EOI & 6 mo.
Rydwik 2008 (55), Rydwik 2010 (56), Lammes 2012 (40)	96	Community-living people receiving home services; Sweden, 60% female.	(1) Aged ≥75, (2) unintentional weight loss ≥5% &/or BMI ≤20 kg/m^2, & (3) low PA level graded with a PA scale.	4-arm RCT: (1) training, (2) nutrition, (3) training & nutrition, & (4) control.	Training: individualised physical training, plus general diet advice. Nutrition: individualised dietary	General physical training advice & general diet advice.	Training: 2 x 1 hr sessions/ wk for 3 mo. 1 x 1 hr dietary counselling session plus 5 group sessions.	EOI, 9 & 24 mo.	**Limb strength** (leg press, dips, pull-down, step ups), **balance** (tandem and one leg stances, step tests), **mobility** (TUG tests,

					counselling &, if appropriate, ONS, plus group education sessions & general physical training advice.				walking speed), RMR, body weight, BMI, **FFM**, fat mass, WC, energy intake and health beliefs at baseline, EOI & 9 mo. **Habitual PA level** & **personal ADL** at baseline, EOI, 9 mo & 24 mo.

[a] - outcome measures in bold are assessed in this review.
[b] - Kandel et al, 2014 full-text not available; information from abstract only.
Abbreviations: ADL, activities of daily living; Ax, assessment; BMD, bone mineral density; BMI, body mass index; CHO, carbohydrate; CRP, C reactive protein; EOI, end of intervention; FFM, fat-free mass; HC, hip circumference;; MFGM, milk fat globule membrane; MMSE, Mini Mental State Examination; MNA, Mini Nutritional Assessment; mo, month; MUAC, mid-upper arm circumference; ONS, oral nutritional supplement; PA, physical activity;; QOL, quality of life; RDA, recommended daily allowance; RMR, resting metabolic rate;; SFT, skinfold thickness; TUG. timed up-and-go; WC, waist circumference; WHR, waist-to-hip ratio.

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Table 2: **Risk of bias summary.**

Study ID	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Blanc-Bisson 2008 (6)	-	?	-	?	?	-	+
Bonnefoy 2003(8)	+	+	-	?	-	-	+
Paw 2001 (50), Paw 2002 (51), de Jong 2000a (20)	?	+	-	-	+	-	+
Fiatarone 1994 (28)	+	?	-	?	+	+	+
Kandel 2014 (35)[b]	?	?	-	?	?	?	?
Kim 2012 (37)	+	+	-	+	+	+	+
Kim 2015(38)	+	+	-	+	+	+	+
Miller 2006(43)	-	+	-	+	-	+	+
Ng 2015 (49)	-	?	-	+	+	+	+
Rosendahl 2006 (53)& Carlsson, 2011 (14)	-	+	-	+	-	-	+
Rydwik 2008 (55), Rydwik 2010 (56), Lammes 2012 (40)	-	?	-	-	-	+	+

Key: + = Low risk of bias; ? = Unclear risk of bias; - = High risk of bias

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Table 3: Summary of findings

Outcomes	Participants (studies), Follow-up	Quality of the evidence (GRADE)	Nutrition & exercise intervention vs. nutrition MD/SMD (95%CI)
Physical functioning			
Handgrip strength	121 (two studies) mean = 2.5 mo	**+++ Moderate** Limited by small number of studies with small sample sizes.	0.22 (95% CI -0.14 to 0.58)
Limb strength	390 (six studies) mean = 3.4 mo	**+ Very low** Limited by some studies with overall high risk of bias of methodological design. Indirectness due to differences in outcome measures, e.g. limb assessed. Inconsistency with some studies showing no effect and others a significant beneficial effect of nutrition and exercise combined.	**FAVOURED NUTRITION AND EXERCISE** 0.33 (95% CI 0.13 to 0.53)
Gait speed	256 (seven studies) mean = 3.2 mo	**++ Low** Limited by some studies with overall high risk of bias of methodological design. Inconsistency with some studies showing no effect and others a significant beneficial effect of nutrition alone.	**FAVOURED NUTRITION** 0.38 (95% CI 0.19 to 0.56)
TUG test	102 (two studies) mean = 3 mo	**++ Low** Limited by one study with overall high risk of bias in methodological design. Limited by small number of studies with small sample sizes	-0.80 (95% CI -2.06 to 0.47)
PAL	182 (three studies) mean = 3.8 mo	**++ Low** Limited by small number of studies with small sample sizes. Indirectness due to differences in intervention duration ranging from 10 weeks to 6 months.	0.04; 95% CI -0.26 to 0.33
Quality of life			
QOL	55 (one study) 3 mo	**+++ Moderate** Limited by small number of studies with small sample sizes and moderate risk of bias of methodological design.	Not estimable
Nutritional status			
FFM	297 (five studies), mean = 3.2 mo	**++ Low** Limited by some studies with overall high risk of bias of methodological design. Indirectness due to differences in outcome measures, e.g. one study used whole-body potassium, others used SFT or body impedance analysis to estimate FFM.	-0.05 (95% CI -0.27 to 0.18)

Abbreviations: CI confidence interval; FFM, fat-free mass; MD, mean difference; mo, month; PAL, physical activity level; QOL, quality of life; SFT, skinfold thickness; SMD, standardised mean difference. TUG, timed up-and-go.

Nutrition and exercise intervention compared with nutrition intervention alone on physical functioning, QOL and nutritional status in sarcopenic, cachexic and/or nutritionally vulnerable older adults.

[a] - **GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group grades of evidence (Balshem et al, 2011 (3)):**
++++ High quality - We are very confident that the true effect lies close to that of the estimate of the effect
+++ Moderate quality - We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
++ Low quality - Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
+ Very low quality - We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

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Appendix 1

Full search strategies for three databases

1.1 Medline

Set	Search terms	Search type	Results
1	**Subject Heading:** Nutritional Support	Advanced	39344
2	**Keywords:** ((nutritional support or diet* or nutrition* or food* or feed* or eat* or meal* or snack* or nutriment* or fortif* or nourish* or enrich* or energy dense or protein dense or nutritional supplement* or oral supplement* or high energy or high protein or nutritionally complete) *NOT* obese or obesity or overweight or type 2 diabetes)	Advanced	1310970
3	**1** or **2**	Advanced	1311422
4	**Subject heading:** Exercise	Advanced	131133
5	**Keywords:** ((exercis* or physical* or activ* or workout* or body build* or gym or sport* or train* or coach* or strength*) *NOT* obese or obesity or overweight or type 2 diabetes)	Advanced	4678094
6	**4** or **5**	Advanced	4707299
7	**Subject heading:** Aged	Advanced	2511168
8	**Keywords:** ((old* or age-old or elder* or senior) *NOT* obese or obesity or overweight or type 2 diabetes)	Advanced	4730689
9	**7** or **8**	Advanced	4787964
10	**3** and **6** and **9**	Advanced	59596
11	**10** and **Refined by: Publication Type**: “Randomized Controlled Trial”	Advanced	6419
12	**11** and **Refined by: Subjects**: “Humans”	Advanced	6248
13	**12** and **Refined by: Subjects**: “Adult”	Advanced	3542
1	**Subject Heading:** Nutritional Support	Advanced	39344

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1.2 Web of Science

Set	Search terms	Search type	Results
1	**Topic:** (nutritional support or diet* or nutrition* or food* or feed* or eat* or meal* or snack* or nutriment* or fortif* or nourish* or enrich* or energy dense or protein dense or nutritional supplement* or oral supplement* or high energy or high protein or nutritionally complete) *NOT* **Topic:** (obese or obesity or overweight or type 2 diabetes or animal or infant or child* or adolescent*)	2709658	**1**
2	**Topic:** (exercis* or physical* or active* or workout* or bodybuilder* or gym or sport* or train* or coach* or strength) *NOT* **Topic:** (obese or obesity or overweight or type 2 diabetes or animal or infant or child* or adolescent*)	2663621	**2**
3	**Topic:** (aged or old* or age-old or elder* or senior) *NOT* **Topic:** (obese or obesity or overweight or type 2 diabetes or animal or infant or child* or adolescent*)	1879950	**3**
4	**1** and **2** and **3**	32199	**4**
5	**4** and **Refined by: Topic:** (randomised controlled trial* or randomised controlled clinical trial* or randomised controlled study or randomised controlled clinical study or randomized controlled trial* or randomized controlled clinical trial* or randomized controlled stud* or randomized controlled clinical stud* randomised-controlled trial* or randomised-controlled clinical trial* or randomised-controlled study or randomised-controlled clinical study or randomized-controlled trial* or randomized-controlled clinical trial* or randomized-controlled stud* or randomized-controlled clinical stud*)	2344	**5**

1.3 Cochrane

Set	Search terms	Search type	Results
1	**Title, Abstracts, Keywords:** nutritional support or diet* or nutrition* or food* or feed* or eat* or meal* or snack* or nutriment* or fortif* or nourish* or enrich* or energy dense or protein dense or nutritional supplement* or oral supplement* or high energy or high protein or nutritionally complete	87072	**1**
2	**Title, Abstracts, Keywords:** exercis* or physical* or active* or workout* or bodybuilder* or gym or sport* or train* or coach* or strength	133472	**2**
3	**Title, Abstracts, Keywords:** aged or old* or age-old or elder* or senior	403362	**3**
4	**1** and **2** and **3**	8857	**4**
5	**4** and *NOT* **Title, Abstract, Keywords:** obese or obesity or overweight or type 2 diabetes or animal or infant or child* or adolescent*	4830	**5**

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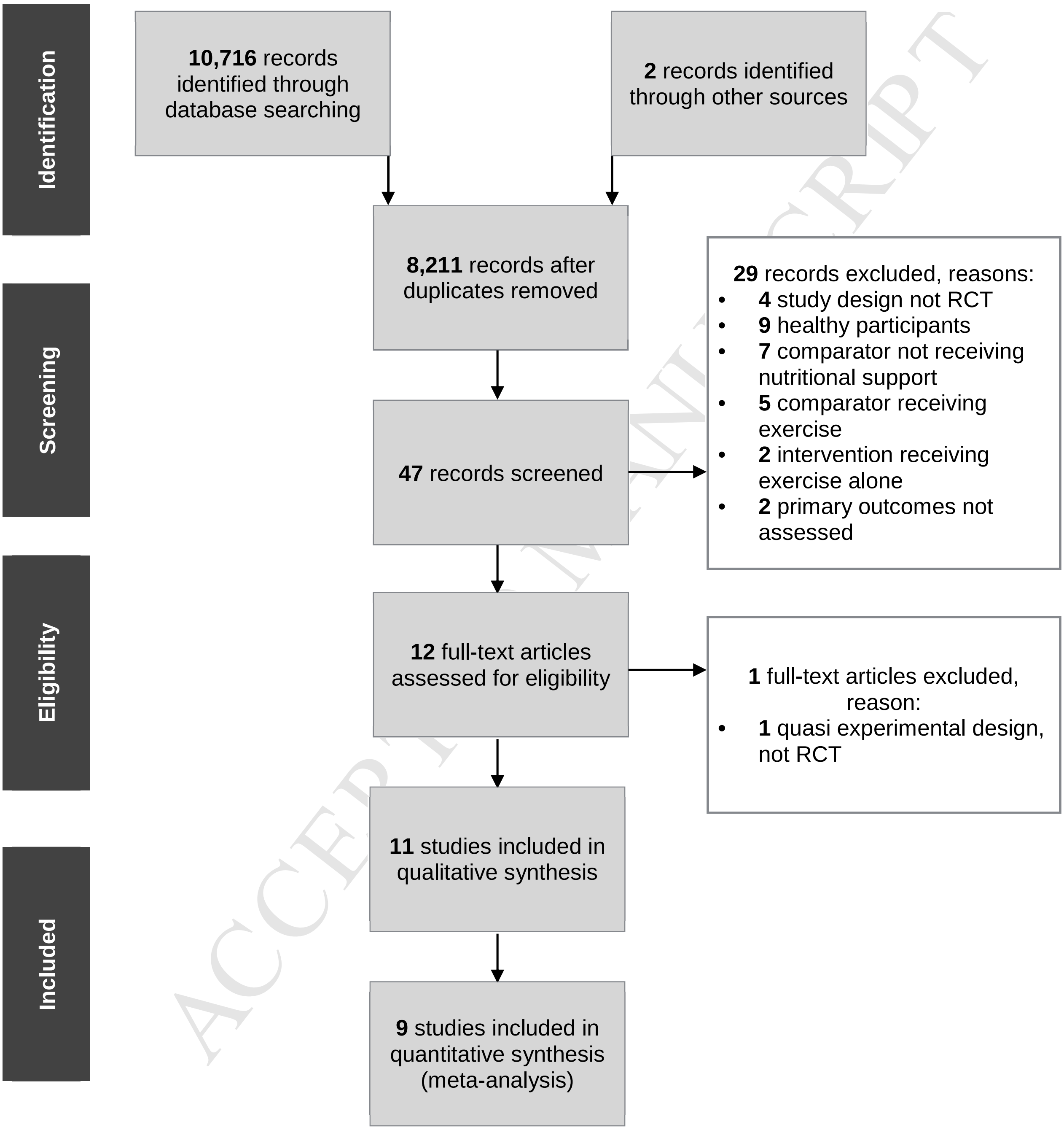
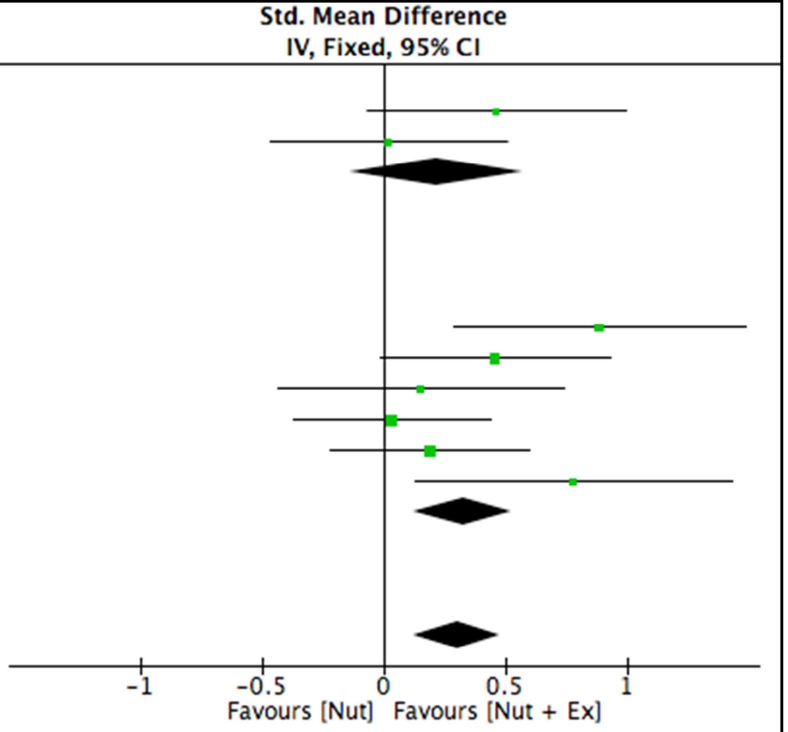
Figure 1:



Abbreviations: RCT, randomised controlled trial.

Figure 2:

Study or Subgroup	Nut + Ex Mean	Nut + Ex SD	Nut + Ex Total	Nut Mean	Nut SD	Nut Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
1.1.1 Handgrip strength								
Kandel et al, 2014	7	12	28	1	13.6	28	10.9%	0.46 [−0.07, 0.99]
Kim et al, 2015	3.9	9.2	33	3.7	12.4	32	13.0%	0.02 [−0.47, 0.50]
Subtotal (95% CI)			**61**			**60**	**23.9%**	**0.22 [−0.14, 0.58]**
Heterogeneity: $Chi^2 = 1.45, df = 1 (P = 0.23); I^2 = 31\%$								
Test for overall effect: Z = 1.20 (P = 0.23)								
1.1.2 Limb strength								
Fiatarone et al, 1994	12.9	12	25	1.4	13.6	22	8.5%	0.89 [0.28, 1.49]
Kim et al, 2012	0.08	0.11	34	−0.01	0.25	37	13.8%	0.45 [−0.02, 0.93]
Miller et al, 2005	1.5	3.71	22	1.1	0.55	23	9.0%	0.15 [−0.44, 0.74]
Pin Ng et al, 2015	1.76	3.82	48	1.64	3.85	47	19.0%	0.03 [−0.37, 0.43]
Rosendahl et al, 2006	11.3	21.2	46	7.1	22.9	46	18.4%	0.19 [−0.22, 0.60]
Rydwik et al, 2008	9	15.59	18	−2.4	13.28	22	7.3%	0.78 [0.13, 1.43]
Subtotal (95% CI)			**193**			**197**	**76.1%**	**0.33 [0.13, 0.53]**
Heterogeneity: $Chi^2 = 8.31, df = 5 (P = 0.14); I^2 = 40\%$								
Test for overall effect: Z = 3.19 (P = 0.001)								
Total (95% CI)			**254**			**257**	**100.0%**	**0.30 [0.13, 0.48]**
Heterogeneity: $Chi^2 = 10.02, df = 7 (P = 0.19); I^2 = 30\%$								
Test for overall effect: Z = 3.37 (P = 0.0008)								
Test for subgroup differences: $Chi^2 = 0.26, df = 1 (P = 0.61), I^2 = 0\%$								



Abbreviations: CI confidence interval; IV inverse variance; SD standard deviation

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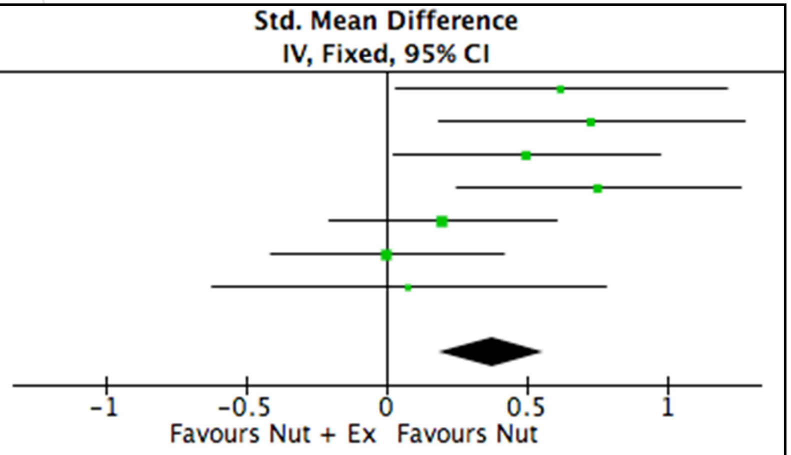
Figure 3

	Nut + Ex			Nut				Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
Fiatarone et al, 1994	0.06	0.1	25	0	0.09	22	10.1%	0.62 [0.03, 1.21]
Kandel et al, 2014	0.13	0.1	28	0.06	0.09	28	11.8%	0.73 [0.18, 1.27]
Kim et al, 2012	0.16	0.16	34	0.06	0.23	37	15.5%	0.50 [0.02, 0.97]
Kim et al, 2015	0.1	0.16	33	-0.05	0.23	32	13.7%	0.75 [0.25, 1.25]
Pin Ng et al, 2015	-0.64	2.26	48	-1.02	1.47	47	21.4%	0.20 [-0.21, 0.60]
Rosendahl et al, 2006	-0.03	0.15	44	-0.03	0.19	46	20.4%	0.00 [-0.41, 0.41]
Rydwik et al, 2008	0.006	0.16	14	-0.01	0.23	18	7.1%	0.08 [-0.62, 0.78]
Total (95% CI)			**226**			**230**	**100.0%**	**0.38 [0.19, 0.56]**

Heterogeneity: $Chi^2 = 9.25$, df = 6 ($P = 0.16$); $I^2 = 35\%$
Test for overall effect: $Z = 3.95$ ($P < 0.0001$)



Abbreviations; CI confidence interval; IV inverse variance; SD standard deviation